PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 30296	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SI 03/00025	International filing date *(day/month/year)* 15.07.2003	Priority date *(day/month/year)* 17.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/20		
Applicant LEK FARMACEVTSKA DRUZBA D.D. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.02.2004	09.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Luangkhot, N Telephone No. +49 89 2399-7857

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SI 03/00025

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 4-8, 10, 11	as originally filed
3, 9	received on 29.11.2004 with letter of 26.11.2004

Claims, Numbers

1-19	received on 29.11.2004 with letter of 26.11.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3
	No:	Claims	1,4-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

1) Amendments

1a) Hand-written new claims 1-19 and amended pages 3, 9 are allowable according to Article 34(2)(b) PCT because a support was found in the description and no subject-matter which extends beyond the content of the application as filed has been introduced.

1b) However word-processed claim 14 is not allowable according to Article 34(2)(b) PCT because no support was found in the description for "a polymer having a viscosity up to **above** 15 mPas". This amendment introduces subject-matter which extends beyond the content of the application as filed.

2) Clarity objection (Art.6 PCT)

2a) The applicant should bear in mind that the examining authority is of the opinion that **the wording in claim 1** "characterized in that it comprises **adding a poor solvent**..." does **not have a precise** meaning and does not mean specifically that it is a humidification step. Therefore he will consider that any process including this step, such as **wet granulation** using a poor solvent wherein the solubility of a substance is less than 0.1g/l, falls within the scope of the subject-matter of claim 1.
The subject-matter of claim 2, which describes a humidification step with water, is far away more appropriate for truly reflecting the subject-matter of present application (humidification followed by drying).

2b) The wording "the polymer used in the coating has a viscosity of over 6 mPas" in claims 16 and 17 is obscure because the experimental **conditions** such as the type of solvent, the concentration, the temperature,... for the measurement of **viscosity** are missing. Therefore it will be considered that the viscosity of the polymer is measured at standard condition, namely with a 2% aqueous solution at 20°C.

2c) Independent claim 1 is directed to a method for a physical pre-treatment of an active substance. The dependent claims 2-11 describe features of the said method.

Claim 12, although dependent on claim 1, is directed to the fact that **pre-treated clarithromycin is used** as starting material for a direct mixture for tableting or encapsulating. This subject-matter is a distinguishable matter to the **pre-treatment process** of claim 1.
The wording of claim 12 is indeed obscure due to **its dependency to claim 1** since this latter refers to a **pre-treatment method of the active substance, not to the use of pre-treated clarithromycin or product containing this latter.**

In order to fulfill the requirement of clarity according to Art.6 PCT claim 12 (use or product claim) should not be dependent on claim 1 (process claim).

Herewith applicant's attention is drawn with the fact that a product is not rendered novel merely by the fact that it is produced by means of a new process. A claim defining a product in terms of a process is to be construed as a claim to the product as such and the claim should preferably take the form "Product X **obtainable by** process Y", or any wording equivalent thereto, **rather than** "Product X **obtained by** process Y" or "Product X **prepared by** process Y".

2d) For the same reasons as in §2d) in order to fulfill the requirement of clarity according to Art.6 PCT, claims 13-16 and 19, related to a **coating** "for pre-treated active substance core", should not be dependent on **pre-treatment process** claim 1 since they are directed to two distinguishing subject-matters.

The present authority will then assum present claims 12-16 and 19 are made independent from the pre-treatment process claim 1.

Re Item IV
Lack of unity of invention

2) This International Examining Authority found multiple (groups of) invention in this international application, as follows:

1. Claims: 1-11 (fully) ,12,17-18 (partially)

Method for physical pre-treatment of an active substance characterized in that

it comprises adding a poor solvent or mixture of solvents to the active substance or mixture of the active substance with other excipients; pharmaceutical formulation containing said pre-treated active substance

2. Claims: 12 (partially), 13-16 (fully), 17-18 (partially), 19 (fully)

A coating for a core of pre-treated active substance; pharmaceutical formulation containing said pre-treated active substance and said coating

1. The application provides solutions to two different technical problems, namely:

a) to modify the technologically important physical properties of an active substance as to enable the manufacture of a formulation having a more stable release profile of the active substance over the whole shelf life of the medicine. The solution proposed is a pre-treatment of the drug by addition of a poor solvent to the drug, preferably humidification with water, followed by drying.

b) to provide a special coating composition because tablet cores of relatively low hardness, such as core containing said pre-treated active substance, are difficult to film-coat. Tablet cores made with the pre-treated drug of a) could be coated with this composition.

The solution of either of these problems was not necessary to solve the other one. It is obviously not necessary to provide a special coating composition to modify the technologically important physical properties of a drug.

Consequently the application foresees the provision of a special coating as an optional feature in the production of a dosage form containing the pre-treated drug. Thus it is not the case that contributing to the solution of one single problem is the feature in the sense of Rule 13.2 PCT that prima facie could unify the claimed subject-matter. Consequently the claimed subject-matter referring to the solution of the first problem and that referring to the solution of the second problem lack unity. The claimed subject-matter therefore does not meet the requirement of Rule 13.1 PCT.

2. The applicant argues that it is not mandatory to include the coating in the

pharmaceutical composition containing a core of pre-treated substance. However the **problems to be solved and the solutions are <u>both</u> distinguishable** (see above). Therefore this application contains 2 inventions.

Furthermore the applicant argues that the features, directed to the coating, are made dependent on a pharmaceutical composition claim, describing a core of pre-treated substance. The present authority does not agree since the **dependency and the wording** of the claims are obscure and at present time inappropriately amended (see herein § 2c/, 2d/ and 6/).

It would be possible to overcome this objection by formulating, provided the requirement according to Art. 34(2)(b) PCT is fulfilled:
- an independent claim which is directed to a tablet, containing a core of pre-treated substance, characterized in that the pre-treatment consists in a humidification of the substance with water, followed by drying (virtual independent claim- not suggested)
- and formulating a dependent claim which specifies that the said tablet may further contain a coating (virtual dependent claim- not suggested).

In this case the application may contain one single invention which is directed to a tablet provided the composition as **originally** suggested above (see "virtual independent claim") is novel and inventive. However a pre-treatment process claim per se, and a coating claim per se may not be claimed **simultaneously (that means in a same application)** as they are directed to **two distinguishable subject-matters devoted to solve two distinguishable problems**.

Furthermore applicant's attention is drawn with the fact that if the subject-matter of the latter virtual independent claim is not novel, i.e. the pre-treatment process is not novel, i.e. the solution suggested to solve the **first** technical problem (see above) is not novel, the feature in the latter virtual dependent claim, i.e. the coating, i.e. the second invention, will be examined regarding novelty and inventive step **only if** the fees for the second invention are paid since the coating belongs to the subject-matter of the second invention.
Put in other words the coating could confer novelty and inventive step to the pharmaceutical composition containing the features of the first invention (already examined), only if the fees for the second invention are paid.

Put in other words if the fees are not paid, the coating as supplementary feature of the pharmaceutical composition, **but also as part of the second invention** will not be examined, and novelty and inventive step could not be recognized.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D5; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

4) Invention 1:

4a) The subject-matter of claim 1, which is directed to a physical pre-treatment of an active substance, characterized in that it comprises **adding a poor solvent**, the solubility of the substance in said solvent being less than about less than 0.1 g/l, **followed by drying**, is nor novel nor inventive because a **wet granulation process** comprising the steps of adding a (poor) solvent then drying, falls within the definition of the subject-matter of claim 1 which is too broadly and unspecifically claimed.

4b) The subject-matter of claim 2, in combination with claim 1, is novel because none of the cited prior art describes a pre-treatment process, wherein the active substance is firstly humidified, then dried. In particular, D1 says that the active substance is dried then humidified (see p.2 L.40-44).

4c) However the subject-matter of claim 2 does not involve an inventive step for lack of evidence and support.

The problem to be solved can be seen as providing a tablet formulation having a more stable release profile of the active substance over the whole shelf life of the medicine. The solution proposed is a pre-treatment of the drug by humidification with water, followed by drying.

However the applicant does not give any evidence that the problems are really existing and are solved by the specific claimed pre-treatment process. Furthermore it seems that the said problems exist only for some specific drugs, i.e. clarythromycin, and not for any drugs, as presently claimed. Therefore the problem is not solved and the subject-matter of claim 2 and its dependent claims does not involve an inventive step.

4d) D2, an other document which can be taken as the closest prior art, describes a pharmaceutical formulation containing **clarythromycin**, characterized in that the drug does not undergo present pre-treatment.

The problem to be solved can be seen as providing a pre-treatment that allows the active substance to be more flowable and compressible, and to enable a formulation with minimized changes in release profile over the shelf life.
The applicant asserts that present pre-treatment will solve the problem.
However he does not give any evidence that the problems are really existing and are solved by the specific claimed pre-treatment process.

The applicant should **provide evidence** (the mere assertion is not enough) with support of tests **compared to the formulation of D2** that the above mentioned problems exist and that the claimed process solves the said problems. Failure to do so would lead to the fact that the claimed process would be considered as **an obvious alternative** that the skilled man in the art would perform by routine without to be faced to any particular technical problem and inventive step would not be acknowledged **over D2**.

Furthermore **it is not at present credible** that the very broadly claimed pre-treatment process would solve the problem over the whole scope. Put in others words it seems that essential features are missing for the definition of the inventiona and it appears that the problem exists only for a specific active substance, namely **clarythromycin**.
Therefore, the applicant is requested to support the present full scope by providing experimental data for several type of solvents, active substances, etc.., or to restrict the scope of the claims to a **reasonable generalisation**.

The applicant argues that present application distinguishes from D2 in that it contains **polysorbate**. However, this feature is not **reflected** in the present claims, nor has it been **searched**.

5) Invention 2:

5a) The cited prior art is not relevant regarding the subject-matter of the second invention. Therefore the subject-matter of claims 13-16 and 19 "might be novel", but does not involve an inventive step for lack of evidence and support (problem not solved).

Furthermore D2, document which can be taken as the closest prior art, mentions a clarythromycin tablet which can be coated with HPMC-phthalate or HPMC (see p.6 L.9-10 and 26-27, and example 6).

The problem to be solved can be seen as providing a film composition that allows to coat a core which is prone to be friable or elastic.
The applicant asserts that present film composition solves the problem (see p.7 L.20-23).
However he does not give any evidence that the problem (difficulty to coat a friable core) is really existing, nor is it solved by the specific claimed film composition.

The applicant is kindly requested **to provide evidence** (the mere assertion is not enough) that the above mentioned problems exist and **with support of comparative tests** that the claimed film composition **solves** the said problems **whereas** the suggested coating formulation of **D2 does not** (coating containing HPMC ;see p.6 L.9-10 and 26-27).
Failure to do so would lead to the fact that the claimed composition would be considered as **an obvious alternative** that the skilled man in the art would perform by routine without to be faced to any particular technical problem and inventive step would not be acknowledged.

5b) In particular the fact that the coating composition contains a combination of polymers with higher and lower viscosity (see present claim 19) does not involve an inventive step because a mixture of polymers with different viscosity is a very well-known technique that the skilled man in the art will carry out in order to obtain a suitable coating composition.

There is no indication supporting the fact that the technical problem can indeed be solved **over the full scope** of the invention, since the applicant does not provide any evidence of the expected effect.
Put in other words **it is not at present credible** that **any combination of polymers** with different viscosity would solve the problem.
Therefore, the applicant is requested to support the present full scope by providing experimental data for several type of polymers, or to restrict the scope of the claims to a **reasonable generalisation**. He should restrict to a specific type of polymer, e.g. HPMC.

In conclusion, in absence of evidence that the stated technical problem can be solved over the full scope claimed, an inventive step cannot be acknowledged for the subject-matter of the second invention.

6) Clarity (Art.6 PCT)

The wording of claim 18 is obscure due to its dependency to claim 1 since this latter refers to a **pre-treatment method of the active substance, not to a process for preparing a tablet formulation**.
The correct rewording of claim 18 would result in claim 17. Therefore claim 18 should be deleted as it would be a mere replication of claim 17.

For the regional phase:

7) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

8) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter **which extends beyond the content of the application as filed.**

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

9) The applicant is kindly requested to take account of the above objections and **give convincing argumentations.** It is **not at present apparent** which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 6.3(b) (I), (ii) PCT (two part form claim). The applicant should also indicate in the letter of reply **the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.**